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Title

Non-small cell lung carcinoma (not otherwise specified) rates are not solely influenced by pathologists' decisions on the use of immunohistochemistry.

Running title

Evaluating immunohistochemistry use in NSCLC-NOS

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GC and DAD collected and analysed data, DAD and WAW designed study. GC, DAD, CDL, WAW contributed to manuscript preparation.

Sir: With increasing focus on the molecular classification of non-small cell lung cancers (NSCLC) to guide therapeutic decisions the correct application of appropriate diagnostic tools is paramount. In small biopsy and cytology specimens the majority can be accurately subtyped on their morphological appearances or with the use of additional immunohistochemistry (IHC), namely thyroid transcription factor-1 (TTF-1) and p63 and/or p40.¹ Despite this, there is still a small proportion in which sub-classification is not possible therefore the category “not otherwise specified” (NSCLC-NOS) remains valid. This can be the result of a ‘null’ IHC phenotype but can also occur in specimens where there are poorly differentiated malignant cells but insufficient material for subsequent IHC.

Both the Royal College of Pathologists and Scottish Intercollegiate Guideline Network (SIGN) guidelines state that NOS rates should be less than 10% of all NSCLC.^{1,2} Recent publication of the ‘LungPath’ project highlighted marked differences between English pathology departments in their rate of NSCLC-NOS (3-20%) with variable application of immunohistochemistry (20-100%).³ The wide variation in the reported use of immunohistochemistry in this study was striking but, whilst informative, the data did not clearly address the issue of whether this related to pathologists’ decisions not to perform IHC or to the nature of the specimen submitted. It therefore prompted us to evaluate the proportion of NOS cases in our department which were as a result of IHC not being requested, non-informative IHC or where insufficient material or unsuitable specimens prevented IHC being undertaken.

The audit was conducted in a regional centre where IHC is routinely requested on small biopsies and cell blocks from cytology specimens only when there is no clear morphological

phenotype. This policy has been in place since 2009 and has reduced our NSCLC-NOS rate for biopsy and cytology specimens to <10%.⁴ In the current audit all patients diagnosed with primary lung cancer from 1st January 2012 to 31st December 2014 were identified using the South East Scotland Cancer Network (SCAN) database. The reports of cases classified as NSCLC-NOS were reviewed to determine specimen type(s), the use of immunohistochemistry and reasons for no further testing. As an audit of clinical practice ethical approval was not required.

Of the 2292 patients identified 159 were coded as NSCLC-NOS. Following review of the reports 38 were excluded due to incorrect data entry leaving 121 cases. The overall rate of NSCLC-NOS for the three-year period examined was 5.3% (Table 1). IHC was performed on 92/121 cases. In keeping with the Royal College dataset recommendations TTF-1 and p63 and/or p40 were used in those cases 100% and 97.8% respectively. In the 29/121 cases where IHC was not performed it was solely due to insufficient material being available. These specimens were all cytology samples, the majority being bronchial brushings/washings (18/29) or fine needle aspirates of either extra-thoracic lymph nodes or metastases (5/29) (Table 1). In all cases there was either insufficient material for a cell block or the prepared block was acellular or contained no malignant cells. No cases were identified where suitable material had been available but IHC was not performed.

Whilst this audit demonstrates a low NOS rate for both histological and cytological specimens it also provides clear evidence that IHC rates cannot be taken in isolation as a satisfactory marker of a pathology department's performance. Understanding the components of the immunohistochemistry "denominator" are therefore essential. Awareness of factors including

specimen type and quality are necessary to reach an accurate conclusion. Guidelines and any proposed College mandatory audits need to reflect and acknowledge likely variation between centres depending on individual case mix, especially where there is more extensive use of cytology for primary diagnosis. Failure to do so may result in pathologists being pressured to over interpret morphological features in cases where no material for IHC is available in order to avoid using the term NSCLC-NOS. What the patient requires is the pathologist to give an honest opinion on the available material and if further more detailed classification is needed then submission of a further specimen may be required. Whilst audits to ensure quality improvement across pathology departments are essential, recognition of factors beyond the pathologist's control is also necessary to ensure an accurate picture is established. Addressing these issues through discussion and education of clinical colleagues with regards to the changing tissue requirements for full pathological and molecular assessment may go some way towards improved sample acquisition and quality.

Table 1. Characteristics of biopsies classified as NSCLC-NOS

	Cases (%)
Total cases	2292
NSCLC-NOS	121 (5.3)
2012	45 (6.0)
2013	37 (4.7)
2014	39 (5.2)
Immunohistochemistry	92 (76.0)
TTF1	92 (100.0)
p63/p40	90 (97.8)
Insufficient for IHC	29 (24.0)
Brushing/washing	18 (62.1)
Needle FNA	5 (17.2)
EBUS FNA	4 (13.8)
EBUS miniprobe	1 (3.4)
Sputum	1 (3.4)

EBUS: endobronchial ultrasound; FNA, fine needle aspirate; TTF1, thyroid transcription factor

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